Fig. 1

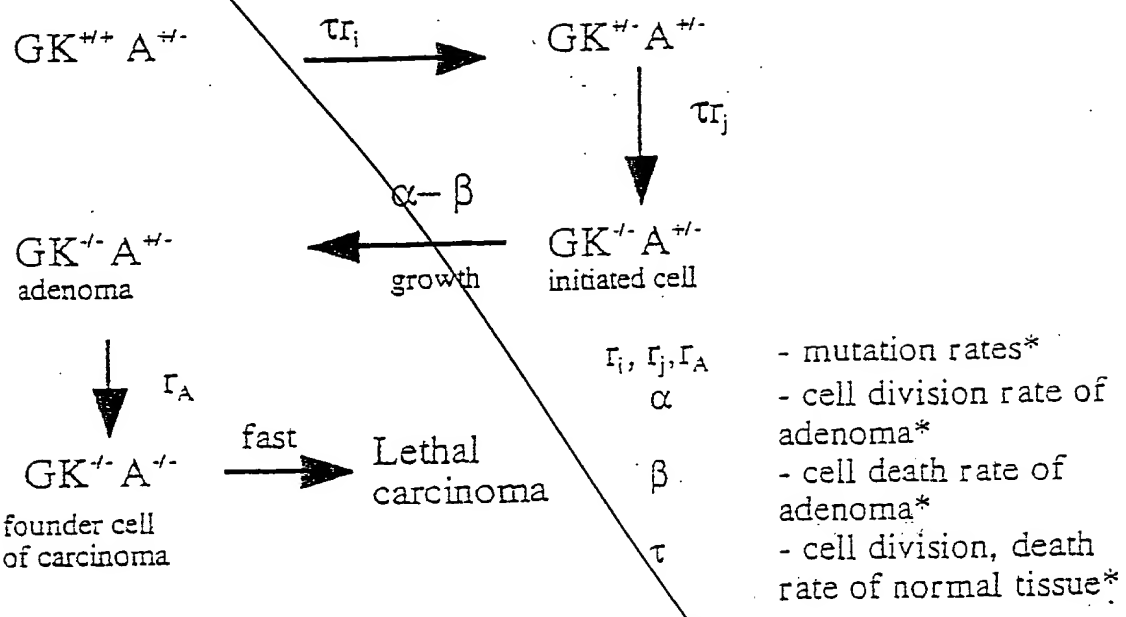

$GK^{+/+}\ A^{+/-}$
τr_i
$GK^{+/-}\ A^{+/-}$
τr_j
$\alpha - \beta$
$GK^{-/-}\ A^{+/-}$
adenoma
growth
$GK^{-/-}\ A^{+/-}$
initiated cell
r_A
$GK^{-/-}\ A^{-/-}$
founder cell
of carcinoma
fast
Lethal
carcinoma
r_i, r_j, r_A - mutation rates*
α - cell division rate of adenoma*
β - cell death rate of adenoma*
τ - cell division, death rate of normal tissue*
* all variables may be affected by exposure, xenometabolism, DNA repair

Fig. 2A

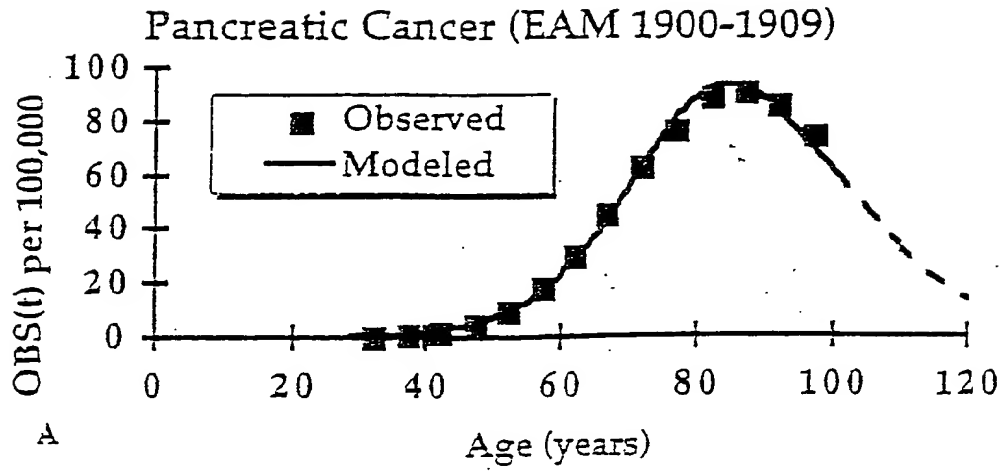

Pancreatic Cancer (EAM 1900-1909)
OBS(t) per 100,000
100
80
60
40
20
0
Observed
Modeled
0
20
40
60
80
100
120
Age (years)
A

Fig. 2B

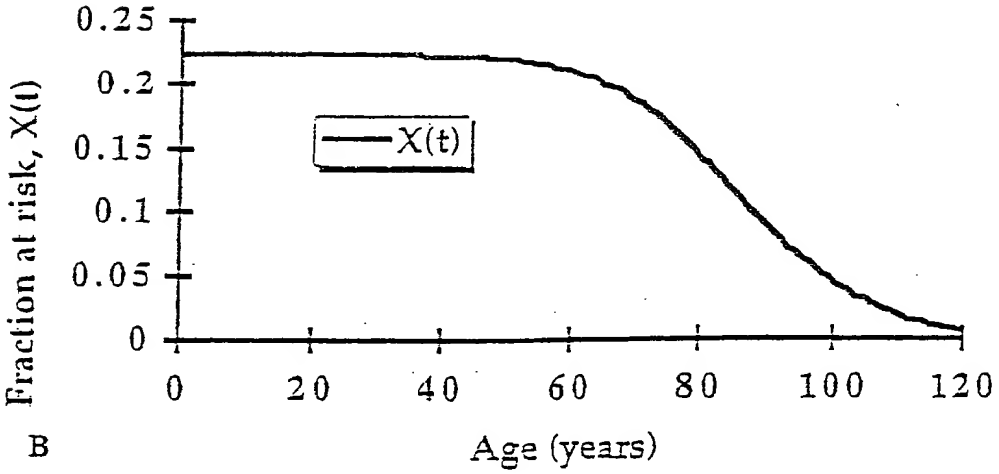

Fraction at risk, X(t)
0.25
0.2
0.15
0.1
0.05
0
X(t)
0
20
40
60
80
100
120
Age (years)
B

Fig. 3A

Fig. 3B

Fig. 3C

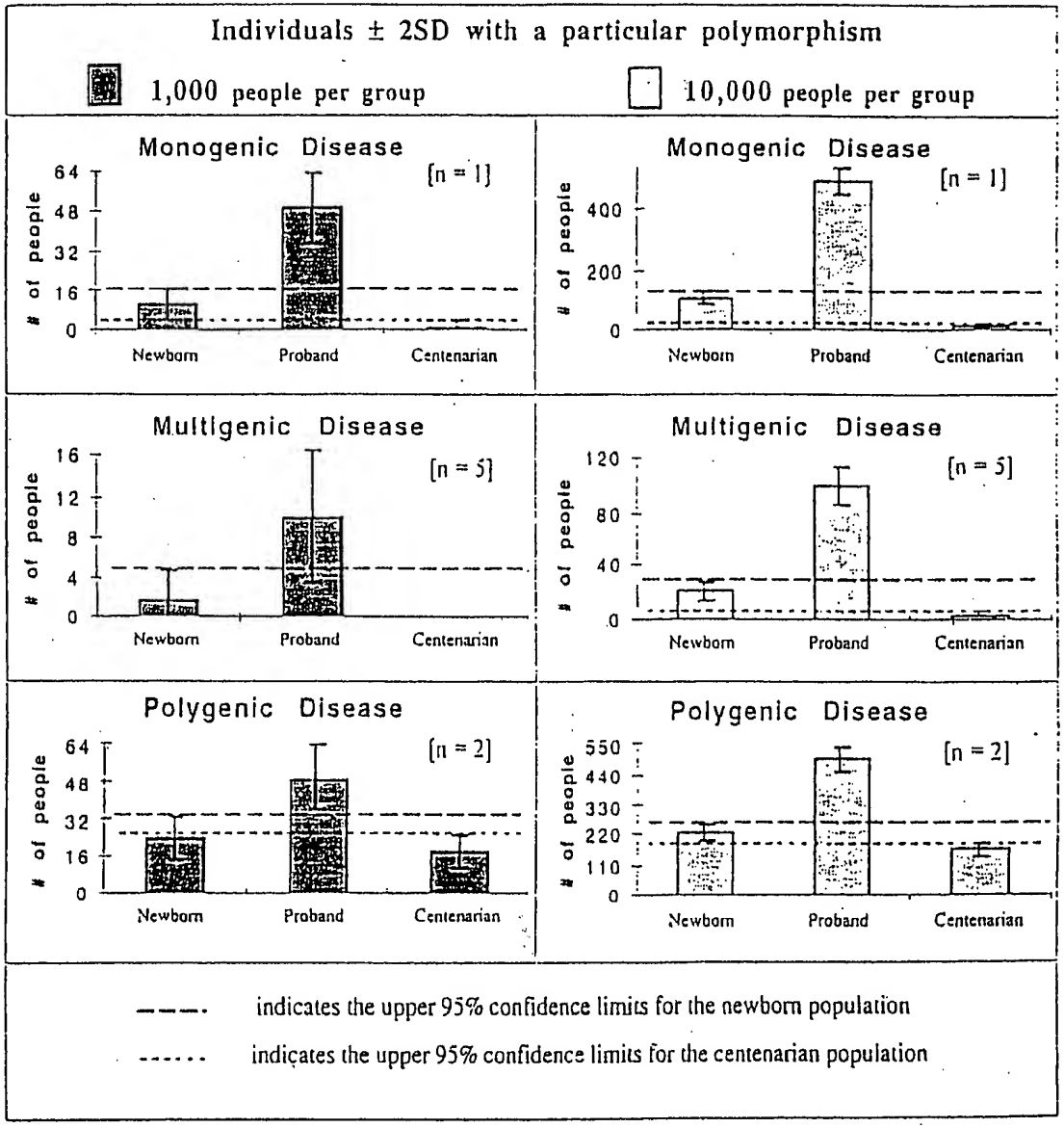


Fig. 3D

Fig. 3E

Fig. 3F

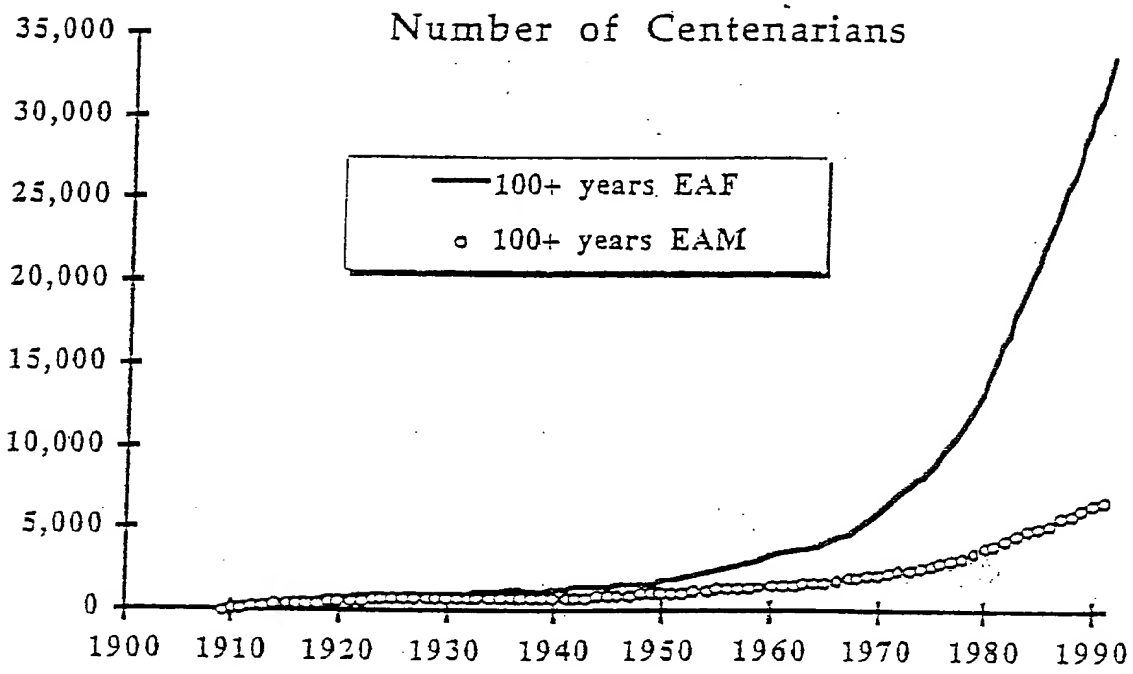
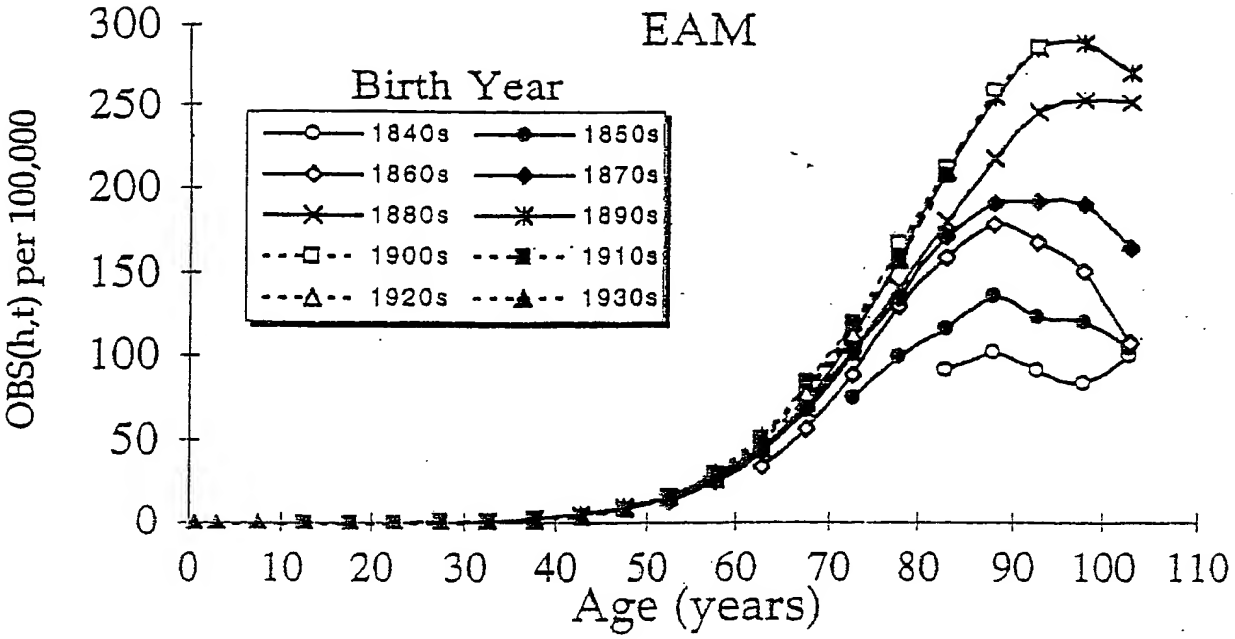

Number of Centenarians
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
100+ years EAF
100+ years EAM

Fig. 4

Fig. 5A


EAM
Birth Year
1840s
1850s
1860s
1870s
1880s
1890s
1900s
1910s
1920s
1930s
OBS(h,t) per 100,000
300
250
200
150
100
50
0
0 10 20 30 40 50 60 70 80 90 100 110
Age (years)

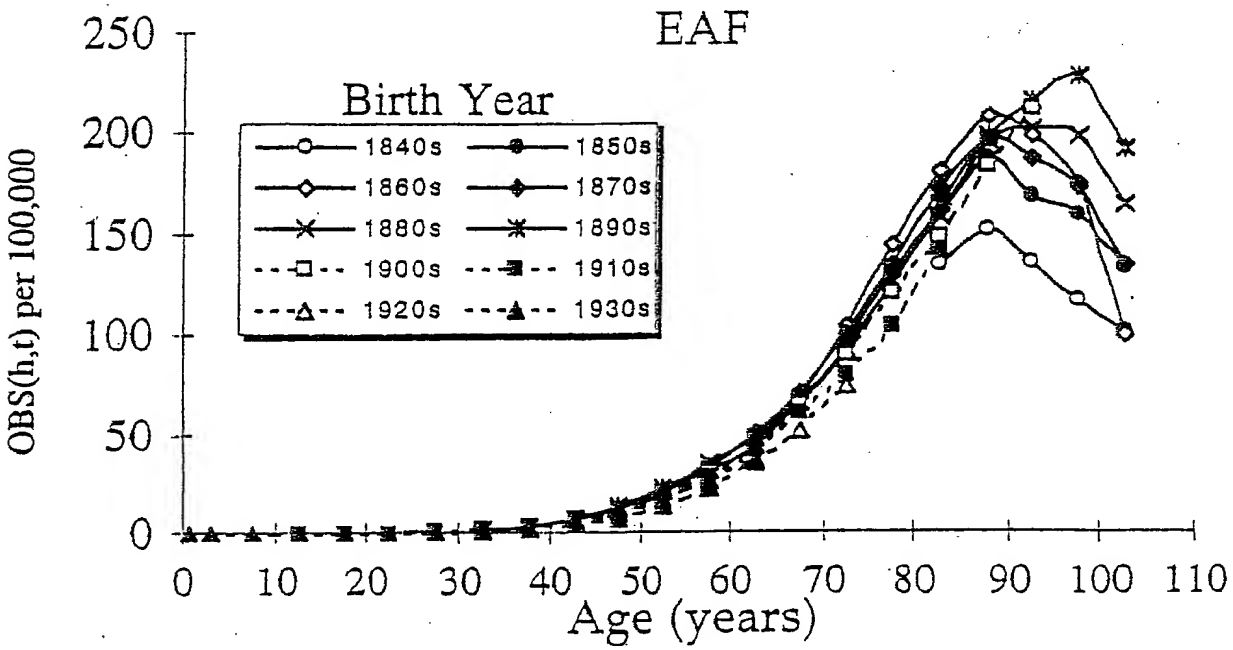
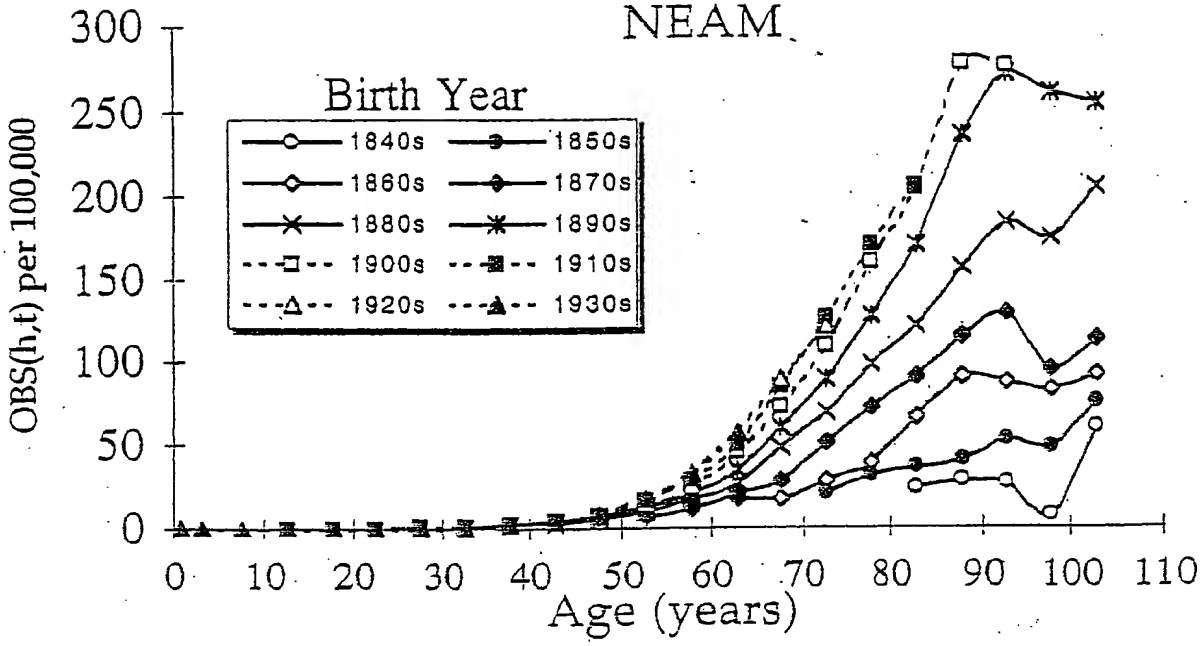

EAF
Birth Year
1840s
1850s
1860s
1870s
1880s
1890s
1900s
1910s
1920s
1930s
OBS(h,t) per 100,000
250
200
150
100
50
0
0 10 20 30 40 50 60 70 80 90 100 110
Age (years)

Fig. 5B

Fig. 6A


NEAM
Birth Year
1840s
1850s
1860s
1870s
1880s
1890s
1900s
1910s
1920s
1930s
OBS(h,t) per 100,000
300
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
90
100
110
Age (years)

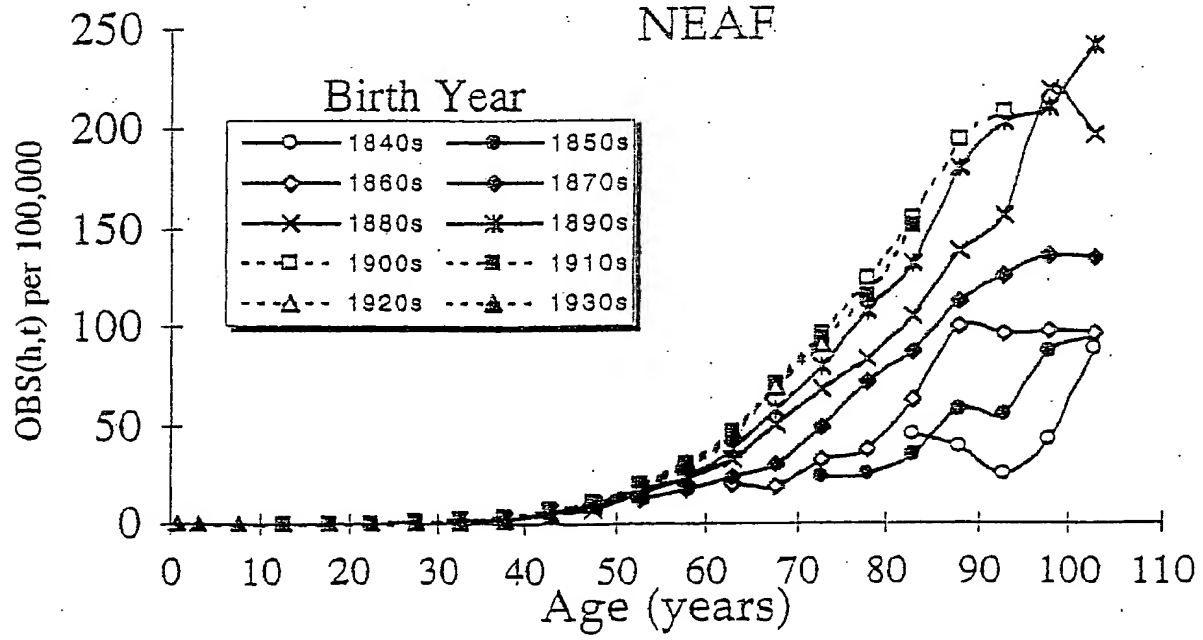

NEAF
Birth Year
1840s
1850s
1860s
1870s
1880s
1890s
1900s
1910s
1920s
1930s
OBS(h,t) per 100,000
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
90
100
110
Age (years)

Fig. 6B

Fig. 7A

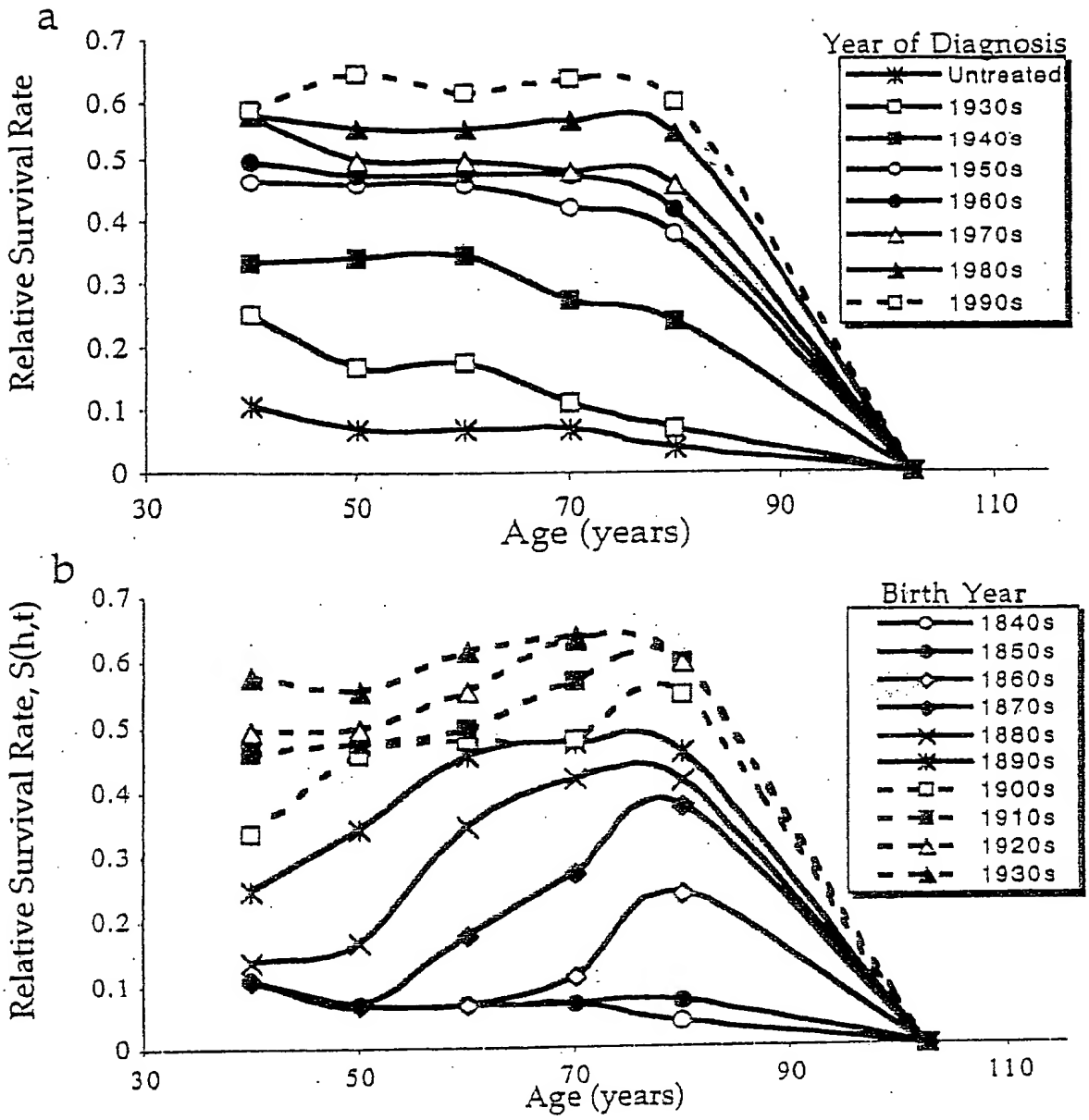

a
Relative Survival Rate
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
30
50
70
90
110
Age (years)
Year of Diagnosis
Untreated
1930s
1940s
1950s
1960s
1970s
1980s
1990s
b
Relative Survival Rate, S(h,t)
Age (years)
Birth Year
1840s
1850s
1860s
1870s
1880s
1890s
1900s
1910s
1920s
1930s

Fig. 7B

Fig. 8

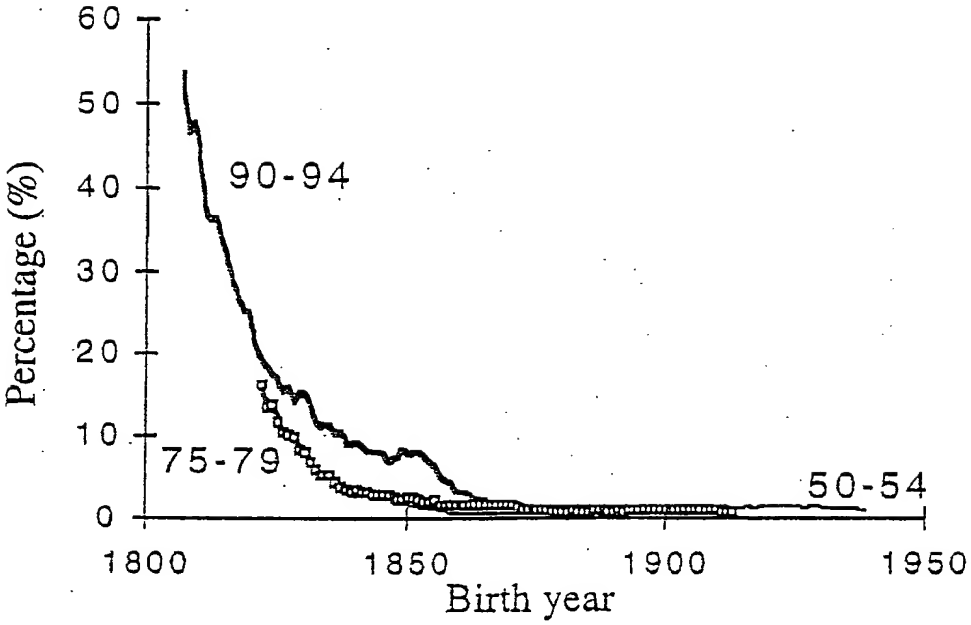
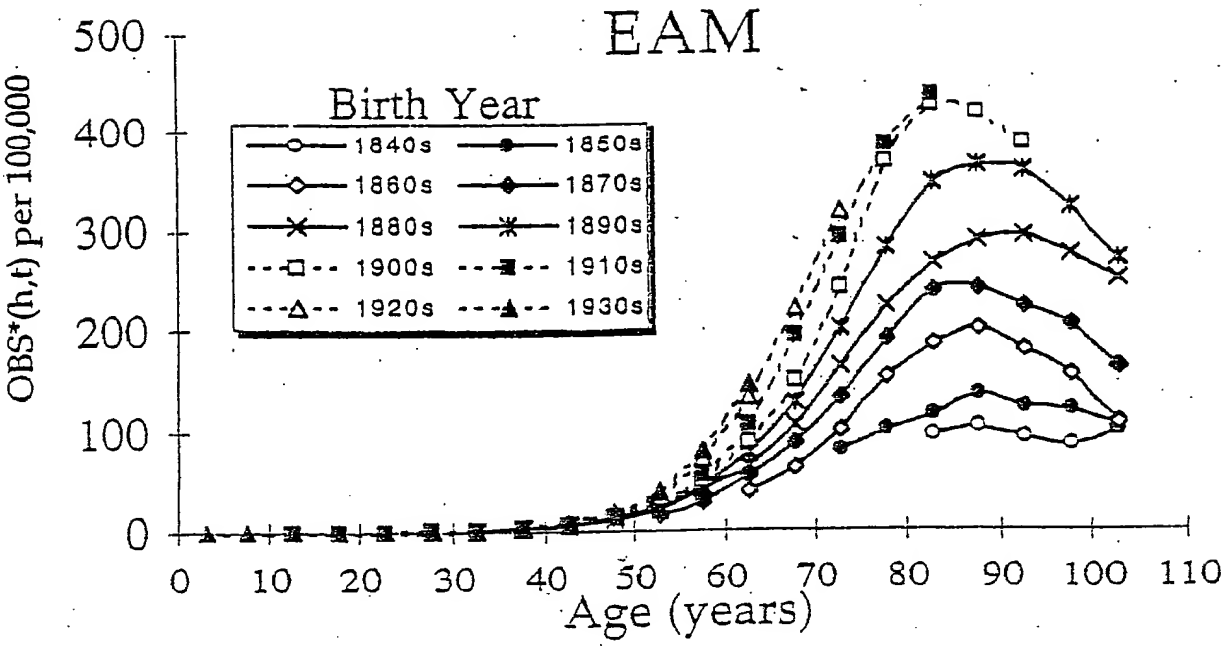

60
50
40
30
20
10
0
Percentage (%)
90-94
75-79
50-54
1800
1850
1900
1950
Birth year

Fig. 9A


EAM
Birth Year
1840s
1850s
1860s
1870s
1880s
1890s
1900s
1910s
1920s
1930s
OBS*(h,t) per 100,000
500
400
300
200
100
0
0
10
20
30
40
50
60
70
80
90
100
110
Age (years)

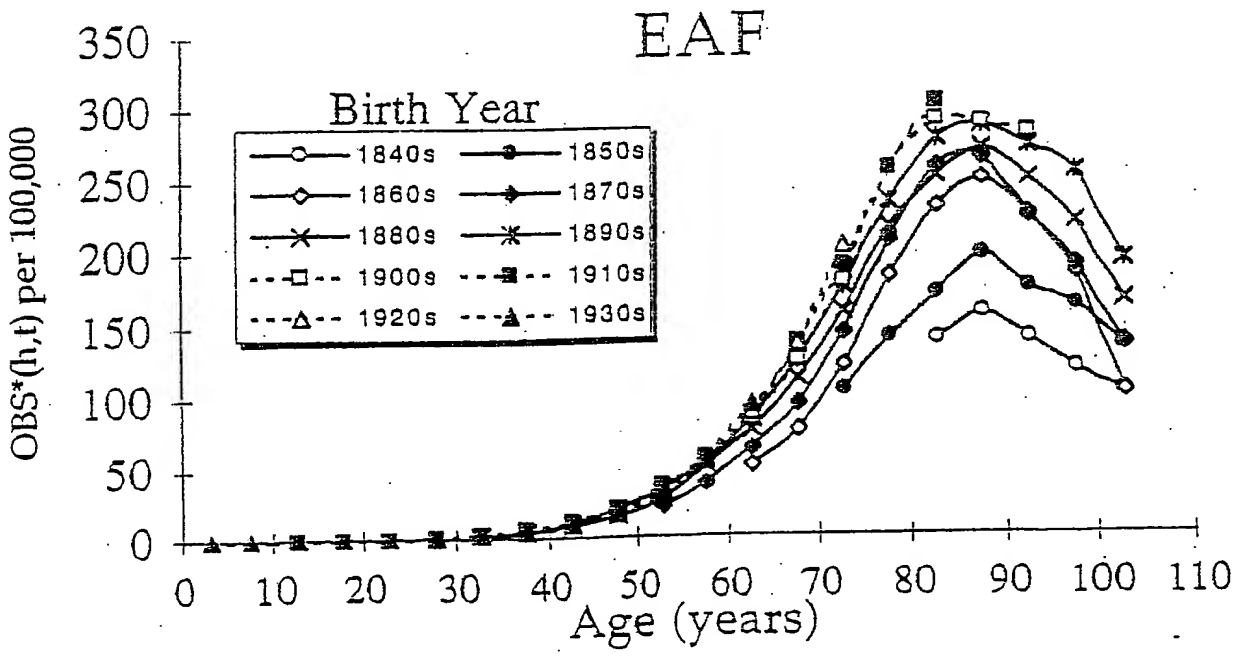
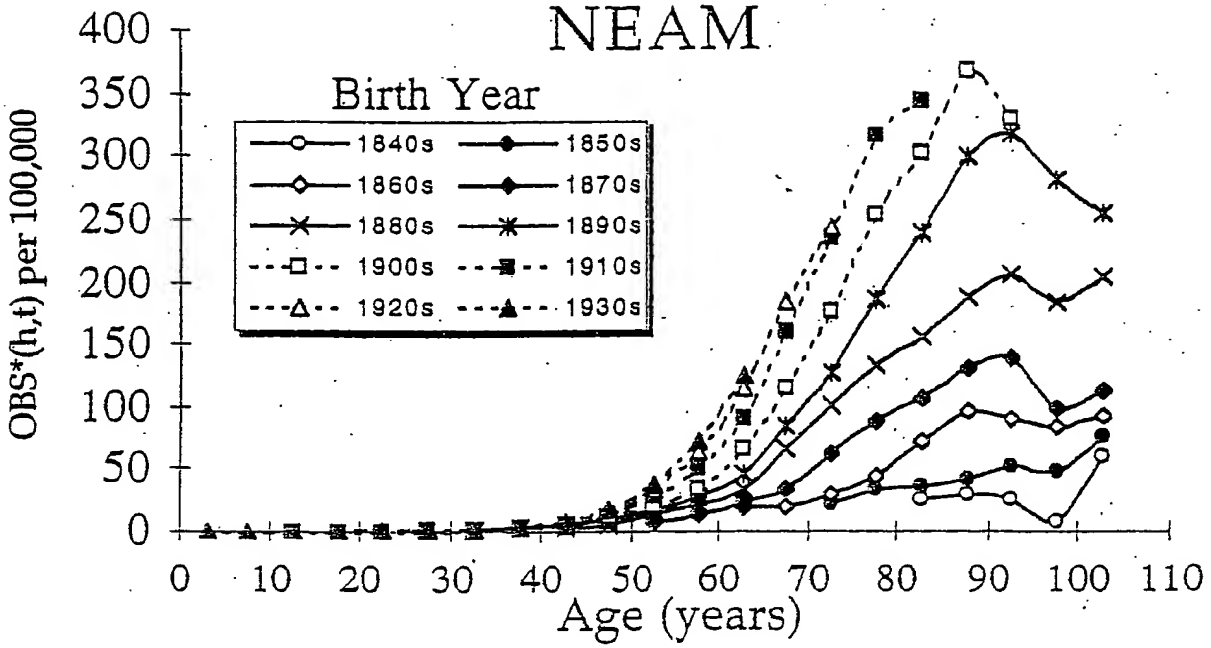

EAF
Birth Year
1840s
1850s
1860s
1870s
1880s
1890s
1900s
1910s
1920s
1930s
OBS*(h,t) per 100,000
350
300
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
90
100
110
Age (years)

Fig. 9B

Fig. 10A



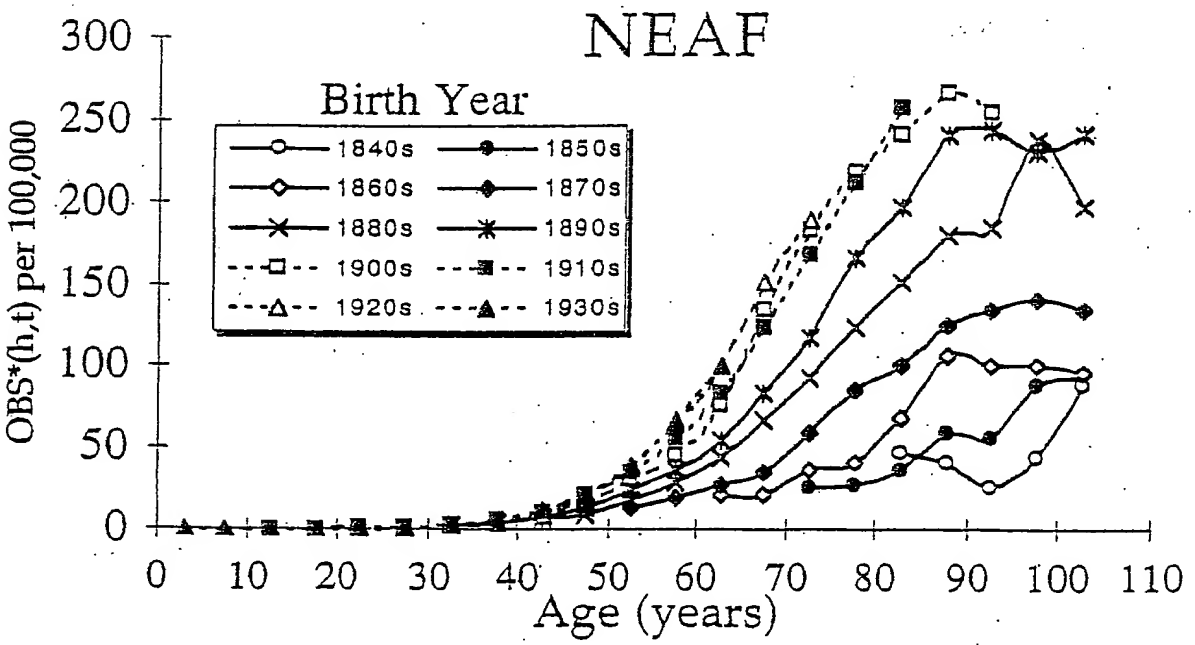


Fig. 10B

Fig. 11A

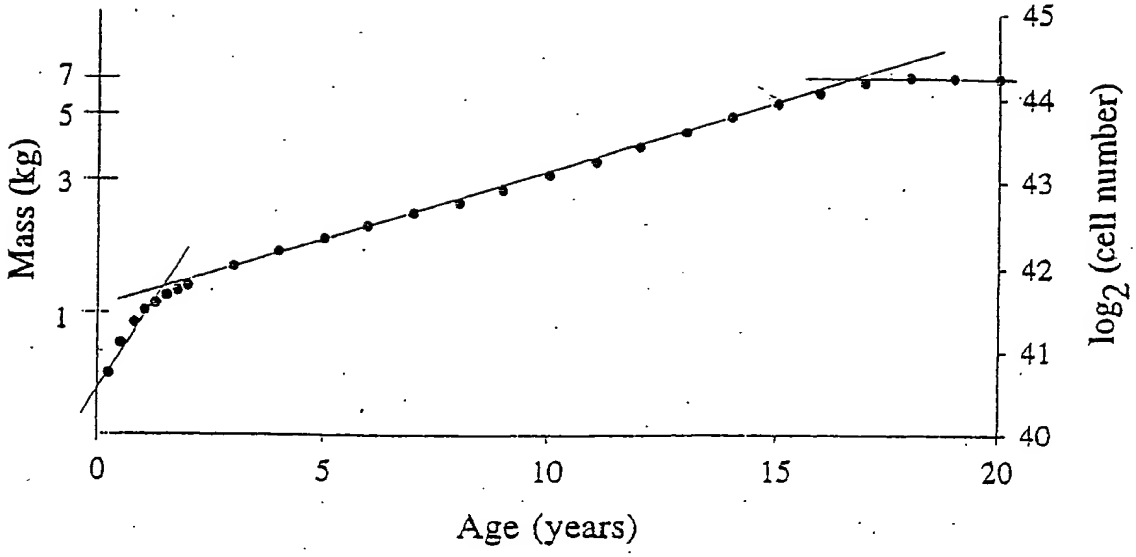
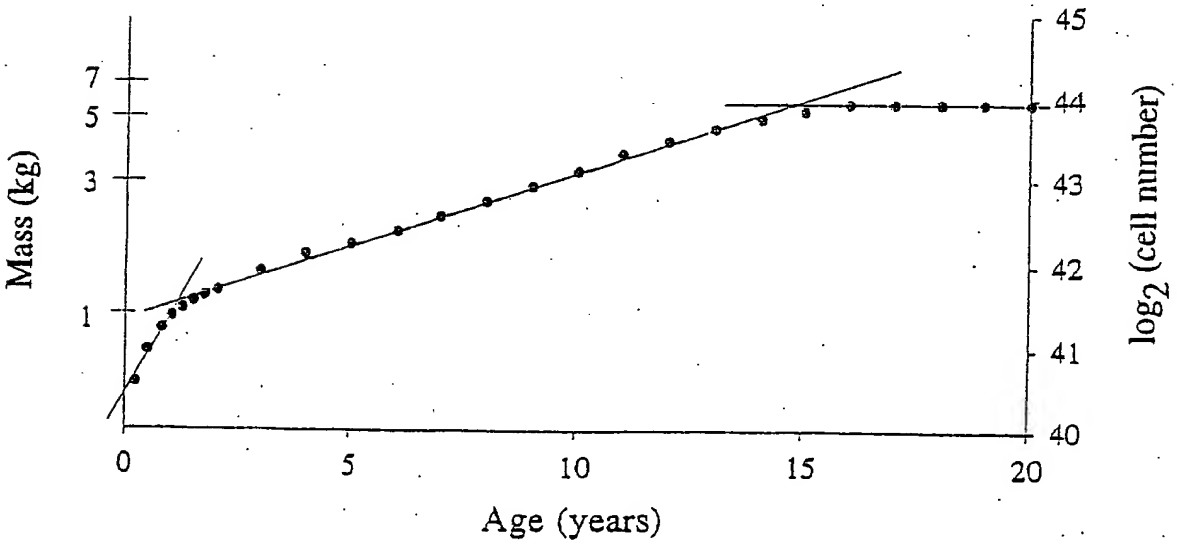


Fig. 11B



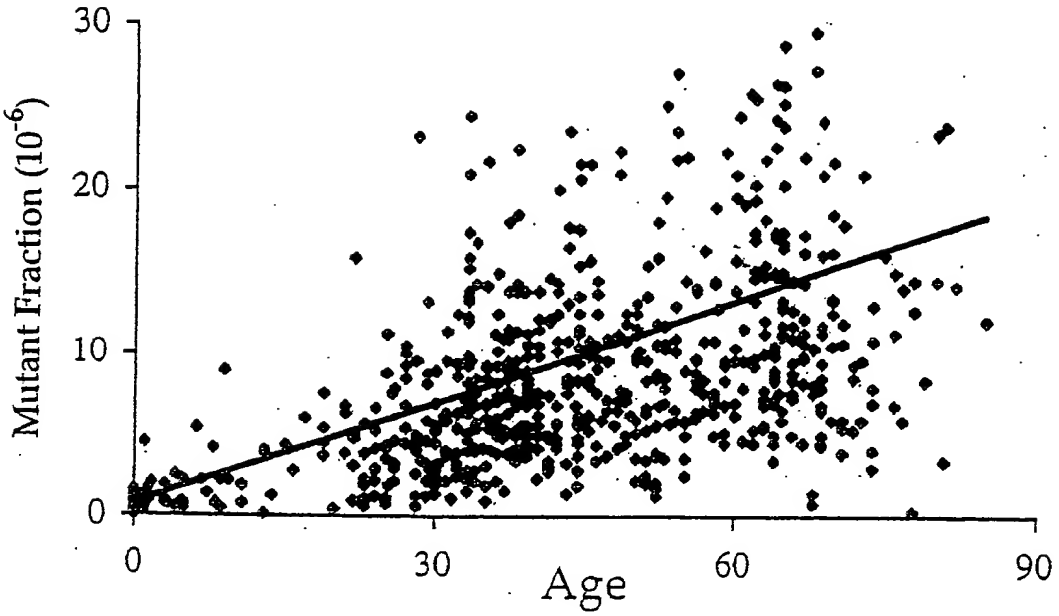

Mutant Fraction (10^{-6})
30
20
10
0
0
30
60
90
Age

Fig. 12

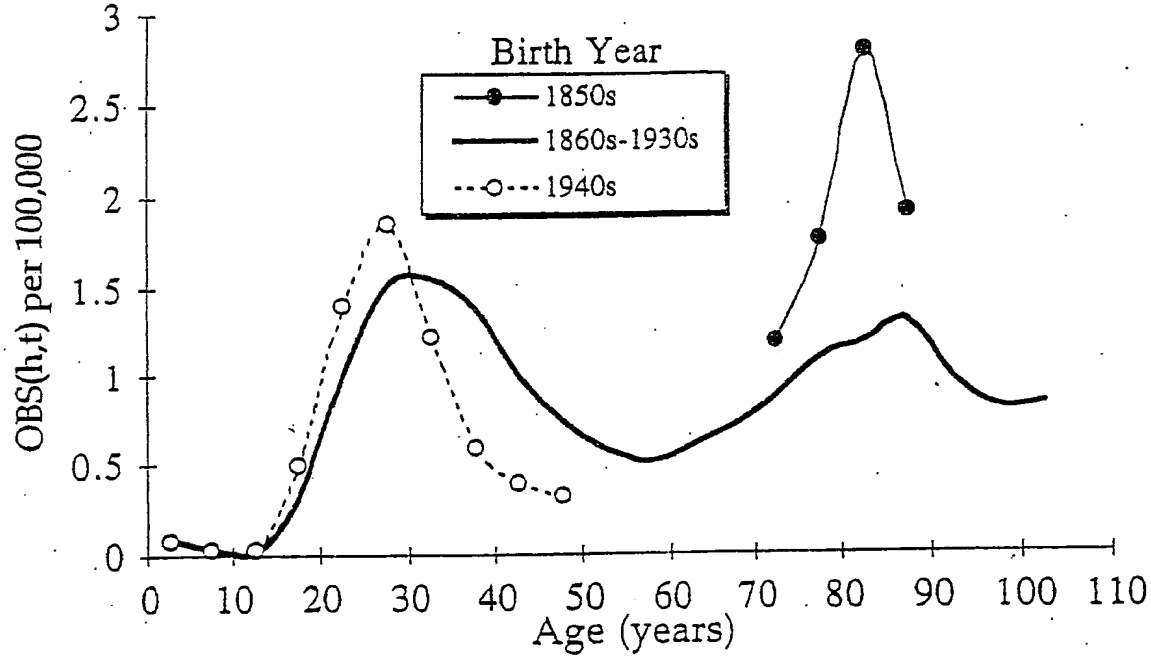
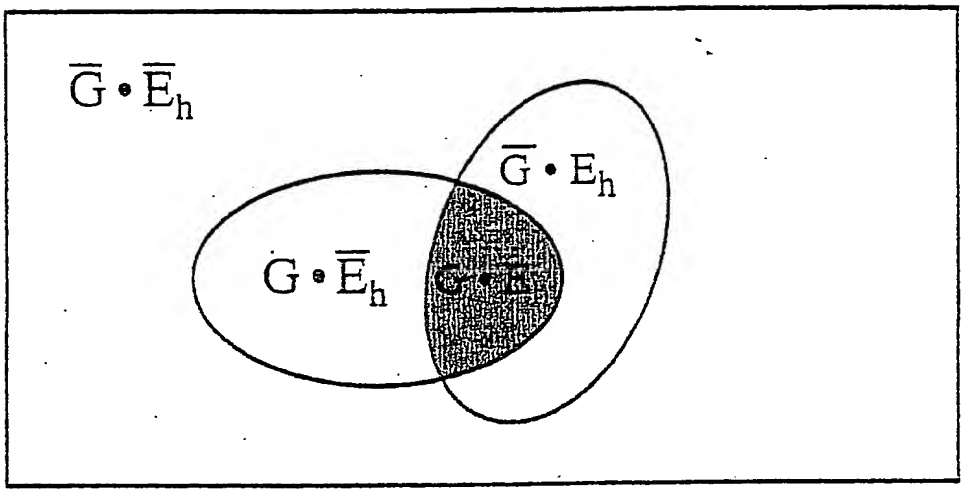

Birth Year
1850s
1860s-1930s
1940s
OBS(h,t) per 100,000
3
2.5
2
1.5
1
0.5
0
0
10
20
30
40
50
60
70
80
90
100
110
Age (years)

Fig. 13

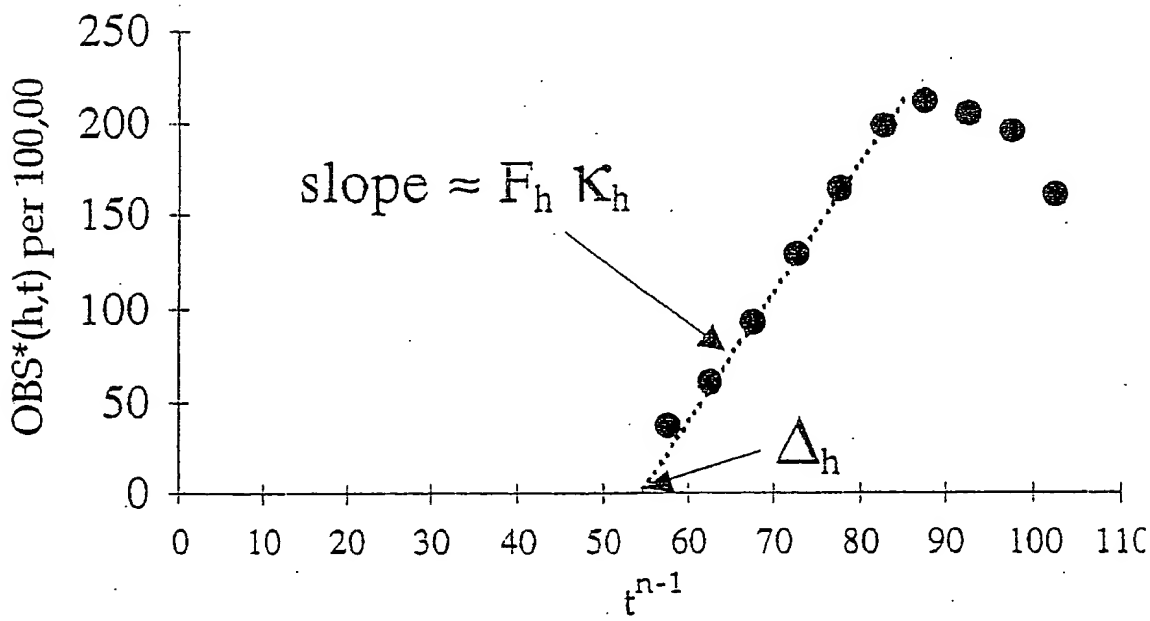
Fig. 14



$G = F(h,t)_{genetic}$ $\quad$ $\overline{G} = (1 - G)$ = not in $F(h,t)_{genetic}$

$E_h = F(h,t)_{environmental}$ $\quad$ $\overline{E}_h = (1 - E_h)$ = not in $F(h,t)_{environmental}$

Fig. 15



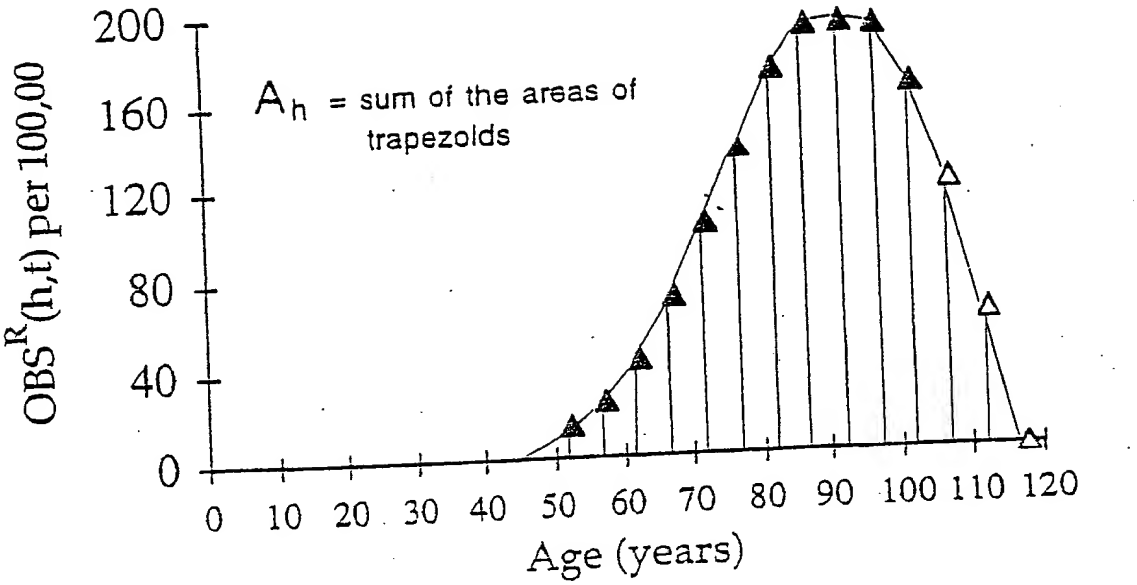

200
160
120
80
40
0
$OBS^R(h,t)$ per 100,00
A_h = sum of the areas of trapezoids
0 10 20 30 40 50 60 70 80 90 100 110 120
Age (years)

Fig. 16

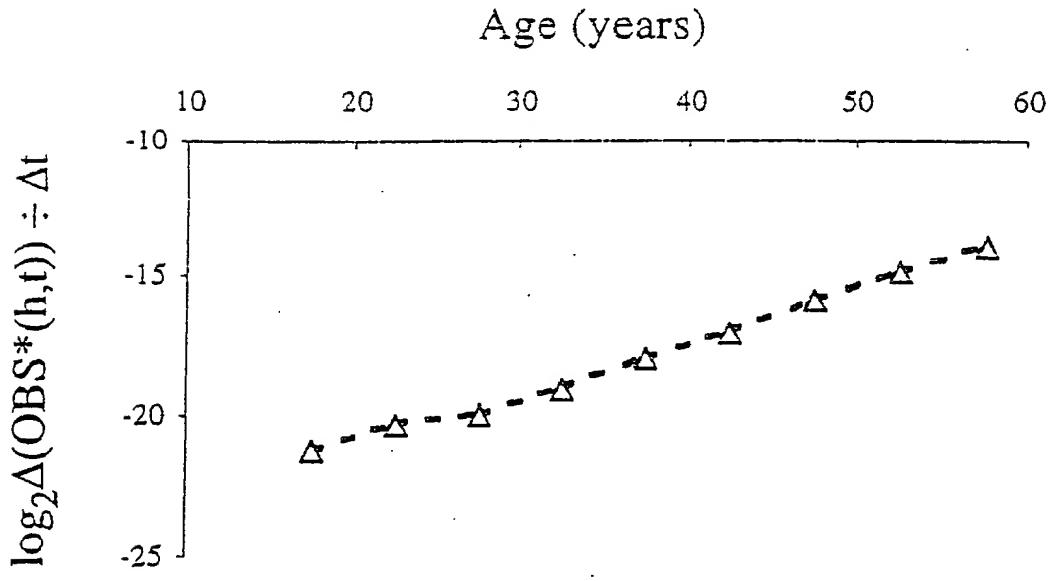

Age (years)
10 20 30 40 50 60
-10
-15
-20
-25
$\log_2\Delta(OBS^*(h,t)) \div \Delta t$

Fig. 17

Fig. 18

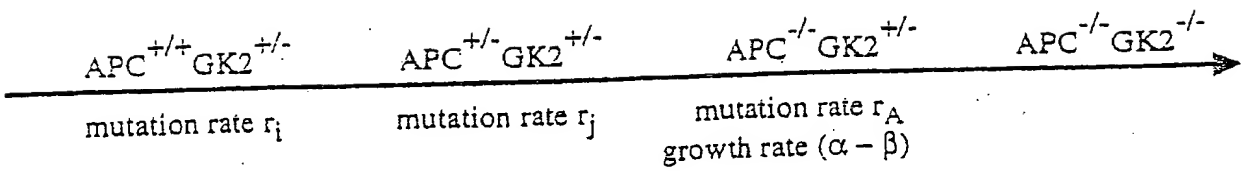

APC+/+GK2+/-
APC+/-GK2+/-
APC-/-GK2+/-
APC-/-GK2-/-
mutation rate ri
mutation rate rj
mutation rate rA
growth rate (α – β)

Fig. 19A

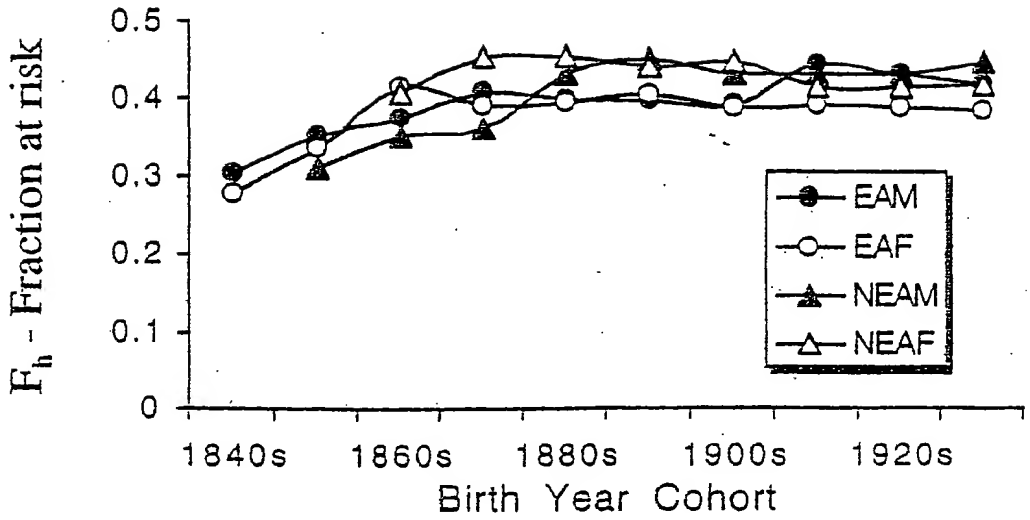


Fig. 19B

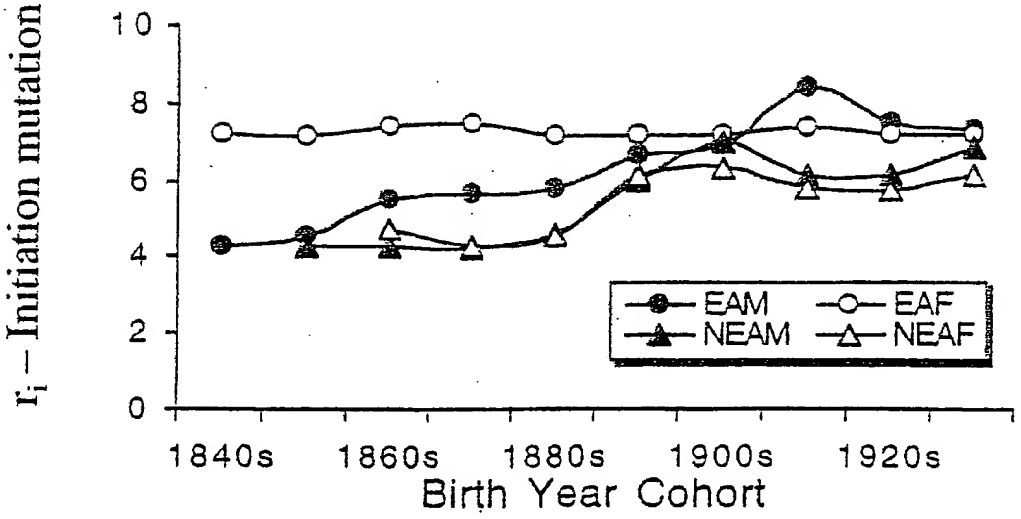


Fig. 20A

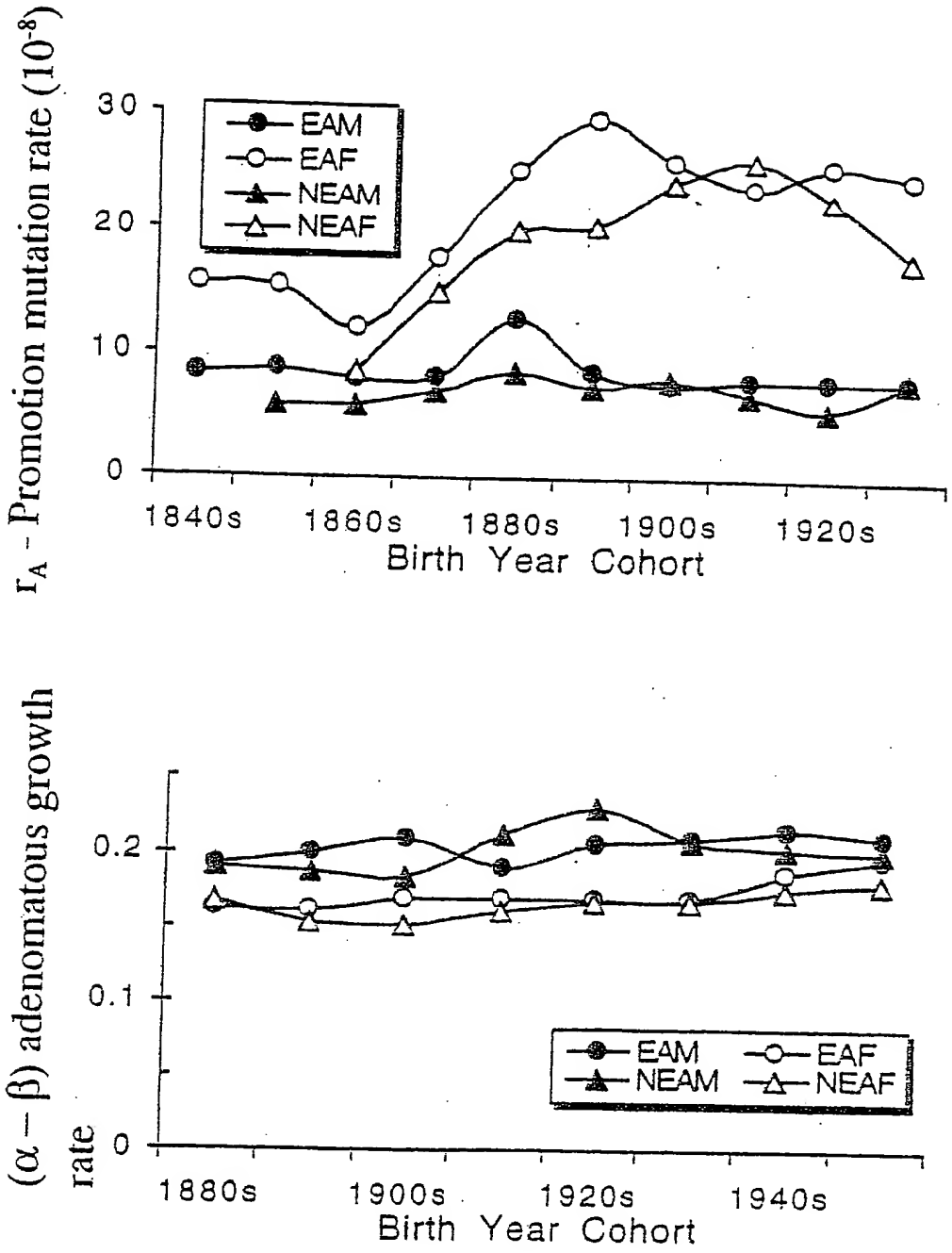


Fig. 20B

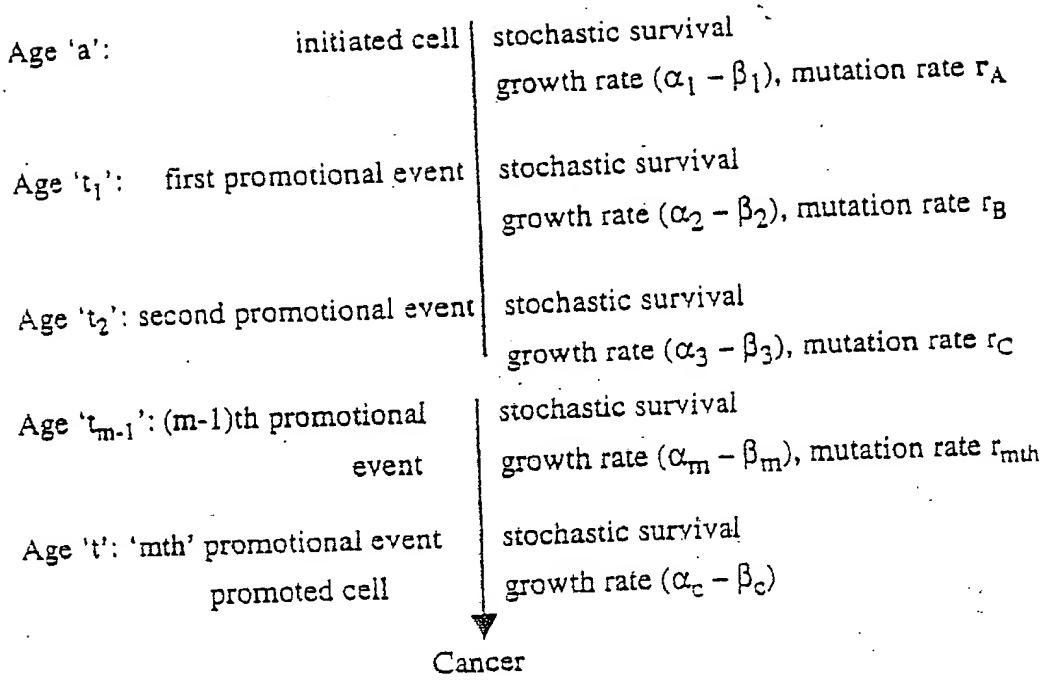

Age 'a': initiated cell
stochastic survival
growth rate ($\alpha_1 - \beta_1$), mutation rate r_A
Age 't_1': first promotional event
stochastic survival
growth rate ($\alpha_2 - \beta_2$), mutation rate r_B
Age 't_2': second promotional event
stochastic survival
growth rate ($\alpha_3 - \beta_3$), mutation rate r_C
Age 't_{m-1}': (m-1)th promotional event
stochastic survival
growth rate ($\alpha_m - \beta_m$), mutation rate r_{mth}
Age 't': 'mth' promotional event promoted cell
stochastic survival
growth rate ($\alpha_c - \beta_c$)
Cancer

Fig. 21

Fig. 22A

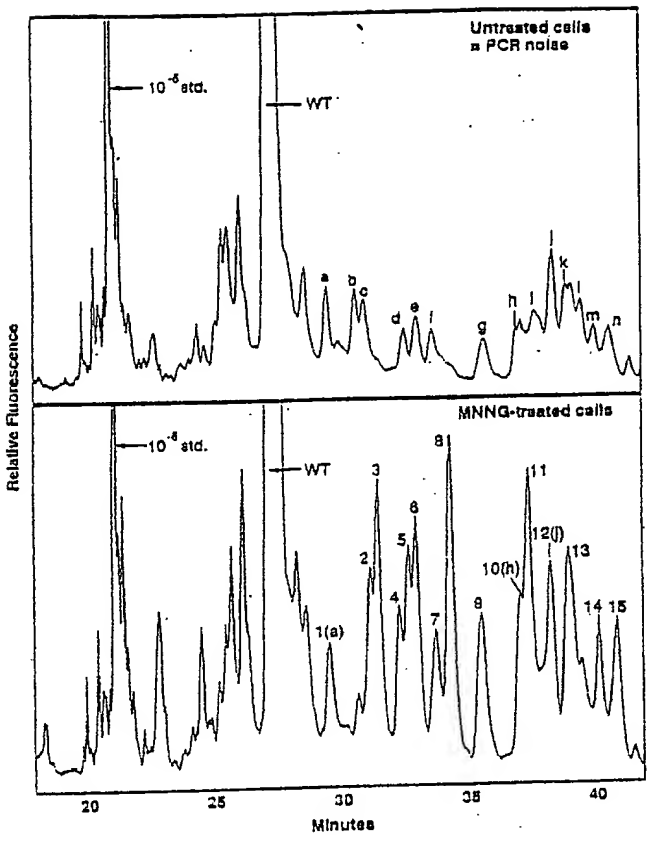


Fig. 22B

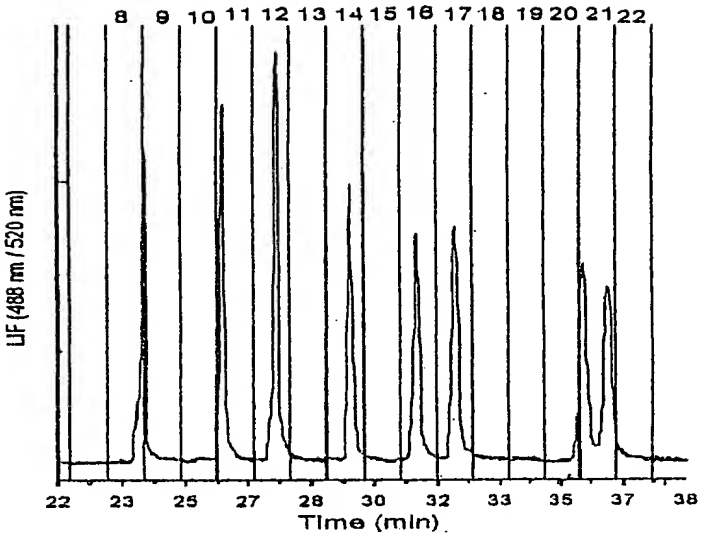


Fig. 23A

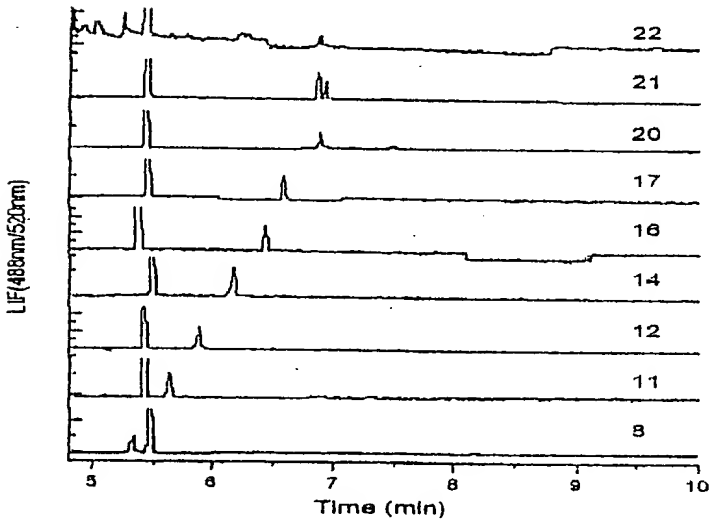


Fig. 23B

Fig. 24

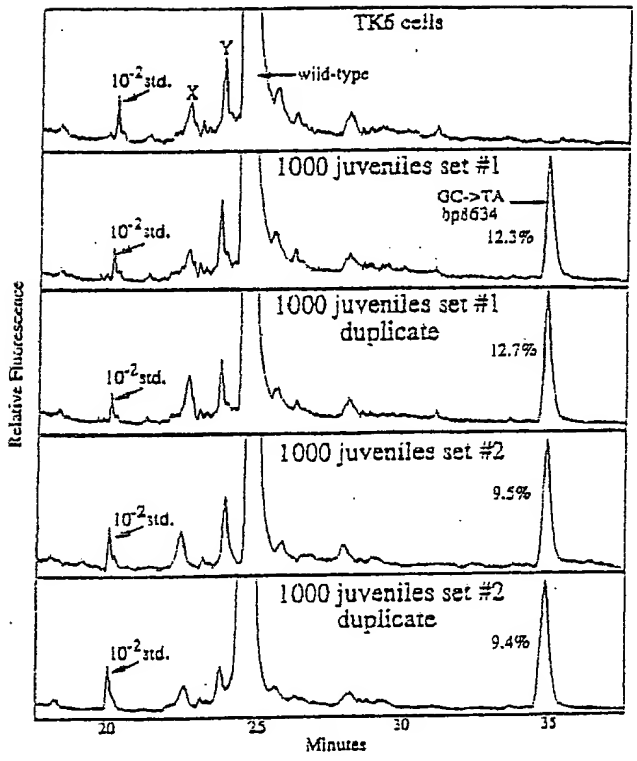

TK6 cells
wild-type
X
Y
10^{-2}std.
1000 juveniles set #1
GC->TA
bp8634
12.3%
1000 juveniles set #1
duplicate
12.7%
1000 juveniles set #2
9.5%
1000 juveniles set #2
duplicate
9.4%
Relative Fluorescence
20
25
30
35
Minutes

Fig. 25

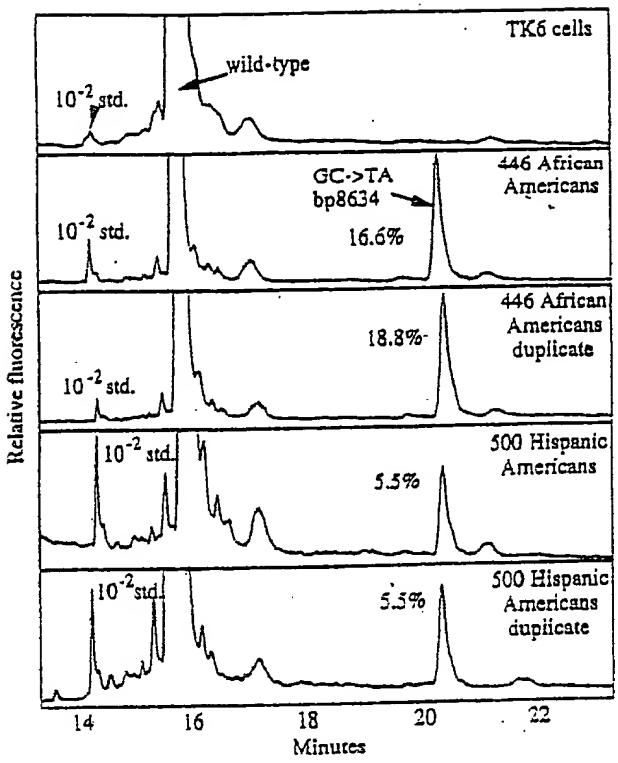


Fig. 26A

Fig. 26B

Fig. 26C

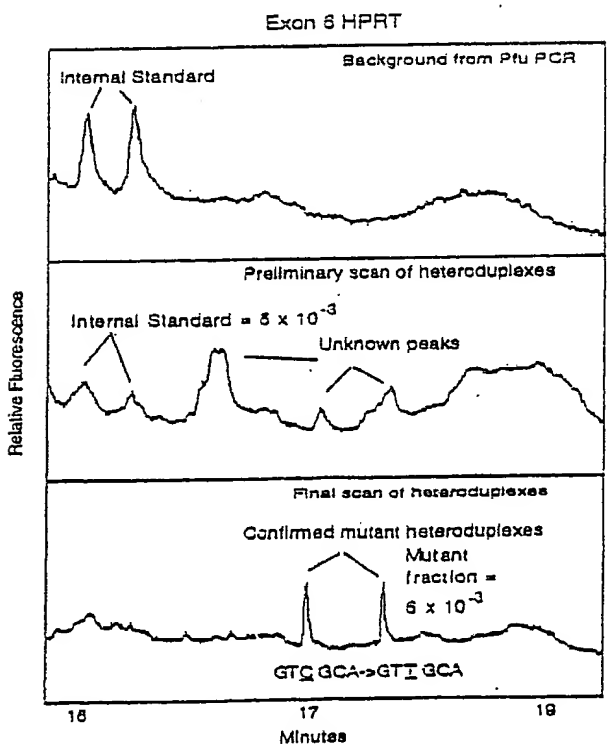
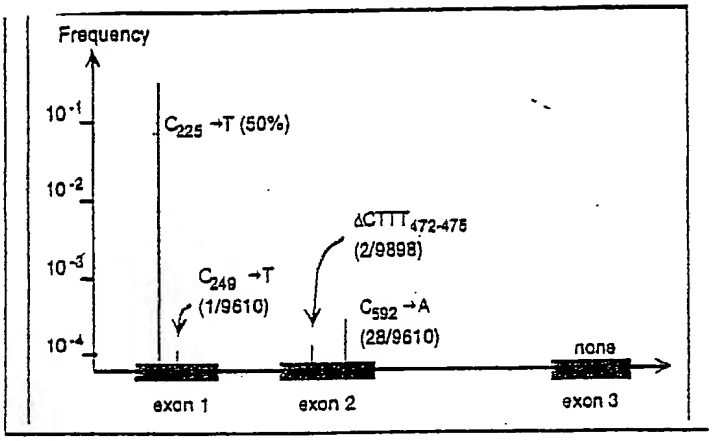


Fig. 27


Frequency
10^{-1}
10^{-2}
10^{-3}
10^{-4}
$C_{225} \rightarrow T$ (50%)
$\Delta CTTT_{472-475}$ (2/9898)
$C_{249} \rightarrow T$ (1/9610)
$C_{592} \rightarrow A$ (28/9610)
none
exon 1
exon 2
exon 3

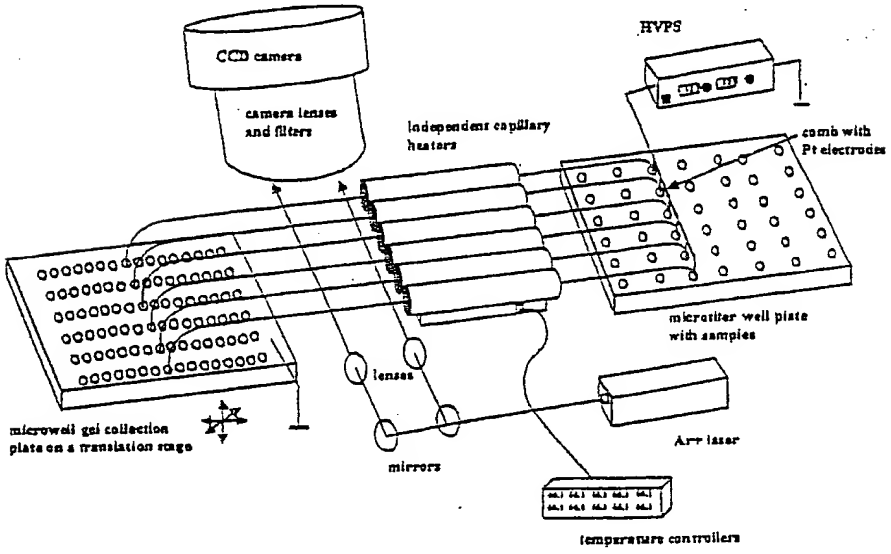
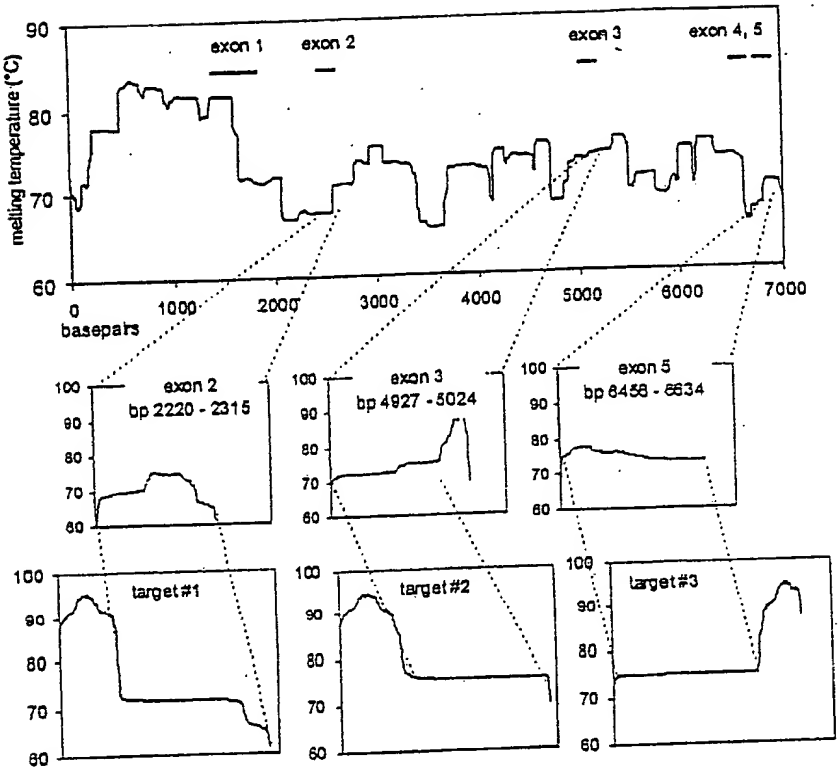

CCD camera
camera lenses and filters
independent capillary heaters
HVPS
comb with Pt electrodes
microtiter well plate with samples
lenses
microwell gel collection plate on a translation stage
mirrors
Ar++ laser
temperature controllers

Fig. 28

Fig. 29




```
 TGCTCCC-agccagcuggCCTAGagaaaaccugAAGGT
                                      T
T                                     T
T       5'3'
 TCGAGGG TCGGTCGACCGGATCTCTTTTGGACTTCCT
```

Fig. 30